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(21) International Application Number: PCT/EP97/03617 (22) International Filing Date: 9 July 1997 (09.07.97) (71)(72) Applicant and Inventor: FORSSMANN, Wolf-Georg [DE/DE]; Blücherstrasse 5, D-30175 Hannover (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): STIEF, Christian, Georg [DE/DE]; Rehmenbreiten 6, D-30966 Hemmingen (DE). TRUSS, Michael, Carsten [DE/DE]; Blücherstrasse 4, D-30175 Hannover (DE). ÜCKERT, Stefan [DE/DE]; Erich-Ollenhauer-Strasse 3, D-30827 Garbsen (DE). JONAS, Udo [DE/DE]; Urologische Klinik, Medizinische Hochschule Hannover, D-30623 Hannover (DE). (74) Agents: MEYERS, Hans-Wilhelm et al.; P.O. Box 10 22 41, D-50462 Cologne (DE).		(81) Designated States: AU, CA, US. Published <i>With international search report.</i>
(54) Title: USE OF PHOSPHODIESTERASE INHIBITORS IN THE TREATMENT OF PROSTATIC DISEASES		
(57) Abstract		
<p>The present invention pertains to the use of inhibitors of phosphodiesterase I, IV and V for the prophylaxis and treatment of prostatic diseases, in particular the use of a) 2-(2-propoxy-phenyl)-8-azapurin-6-one (zaprinast); b) dipyridamole; c) 1-(3-chlorophenylamino)-4-phenylphthalazine (M5445); d) 2-(N-(4-carboxypiperidine-6-chloro-4-(3,4-(methylenedioxy)benzyl)amino)quinazoline (E 4021, ER 21355); e) 2,3-dihydro-8-hydroxy-7-nitro-1,4-benzodioxine-2-methanol, alpha-nitrate (E 4701); f) 4-((3,4-(methylenedioxy)benzyl)amino)-6,7,8-trimethoxy-quinazoline; g) 1-methyl-3-propyl-6-(5-(N-(4-methylmorpholino)sulfonyl)-2-ethoxyphenyl)pyrazole [4,5]pyrimidin-4(5H)one (sildenafil); i) 1-cyclopentyl-3-methyl-6-(4-pyridinyl)pyrazolo(3,4-d)pyrimidin-4(5H)-one (WIN 58237); j) 7-(3-(4-acetyl-3-hydroxy-2-propyl-phenoxy)-2-hydroxy-propoxy)-2-carboxy-2,3-didehydro-chroman-4-one (FPL-557212); k) quinazolines and their trimethoxy derivatives; l) Pyrazolopyrimidones; as well as pharmacologically compatible salts thereof, quinazolines and their trimethoxy derivatives, pyrazolopyrimidones or compatible salts thereof, in local and systemic administration.</p>		

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Use of Phosphodiesterase Inhibitors in the Treatment
of Prostatic Diseases

The prostate gland is an organ of about chest-nut size which in males surrounds the cervix of the vesical outlet. In 50% of the males in the age of above 50 years, a benign growth of the prostate gland occurs which may result in severe difficulties in the miction up to anuria and which is subject to treatment obligation. Most of the affected patients must be treated with surgical methods.

In the development of benign prostatic hyperplasia (BPH), the glandular portions of the prostate gland increase by double their volume, and the muscular and fibrous portions increase by four times their volume (Christmas and Kirby, W.J. Urol. 9: 36-40, 1991). Since these muscle cells account for a large portion of the total prostatic tissue (at least 35%), a distinct improvement of miction can be achieved by means of a pharmacologically induced relaxation of these muscle cells (Hedlund and Andersson, J. Urol. 130: 275-278, 1983). The substances used to date mostly belong to the group of alpha-receptor blockers (Lepor et al., J. Urol. 143: 267, 1990), or they interfered with the hormonal regulation of the prostate gland (Kirby and Christmas, W.J. Urol., 9: 41-44, 1991); these medicament treatments were characterized by either a very low effectiveness, a slow onset of action, or significant side-effects, or a combination of such effects.

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Therefore, we have examined a completely different pharmacological principle of action, namely the affection of a key enzyme within the smooth muscle cells of the prostate gland, phosphodiesterase.

The physiological transmission of information for the relaxation of smooth muscle cells is effected by messengers of the blood (hormones) or the nerves (neurotransmitters). These messengers and neurotransmitters cause an increase in the levels of the cyclic nucleotides "cyclic adenosine monophosphate" (cAMP) and "cyclic guanosine monophosphate" (cGMP) in the smooth muscle cell, resulting in relaxation. cAMP and cGMP themselves are hydrolyzed by phosphodiesterases (PDEs). Inhibitors of the PDEs in turn reduce the digestion of cAMP and cGMP, resulting in an increase of these molecules within the cell and thus in a relaxation of the smooth muscle cell. This mechanism of action has been described, for instance, by C.D. Nicholson, R.A. Challiss, and M. Shadid: *Trends Pharmacol. Sci.*, 12 (1991), 19-27, C.D. Nicholson and M. Shadid: *Pulm. Pharmacol.* 7 (1) (1994), 1-17, and T.J. Torphy et al.: *J. Pharmacol. Exp. Ther.* 265 (3) (1993), 1213-23.

From these publications as well as from W.J. Thompson: *Pharmacol. Ther.* 51 (1991), 13-33, and J. Beavo in: J. Beavo and M.D. Housley (eds.): *Cyclic nucleotide phosphodiesterases: Structure, regulation and drug action*, Chichester, New York-Brisbane-Toronto-Singapore, Wiley, 1990: 3-15, there is further known the distinction of a number of subtypes of PDE, the specific phosphodiesterases (sPDE). There is distinguished between five different sPDEs which are differently distributed in the individual organs and organ systems and exhibit different levels of effectiveness according to their distribution. In the publications mentioned, there is also discussed the occurrence of the different isoenzymes in various tissues.

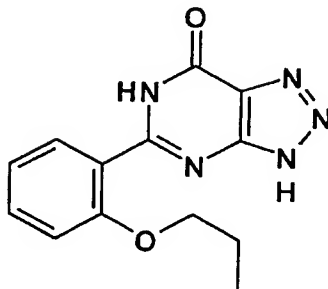
An interesting target for the use of PDE isoenzyme selective inhibitors is the lower urinary tract since the medicamental therapy of prostate dysfunctions with conventional substances is often little effective and full of side-effects. Therefore, a well-aimed affection of the prostatic muscles by inhibiting a functionally important sPDE isoenzyme appears to be superior to conventional therapy methods.

Surprisingly, it has now been found that sPDE I, sPDE IV and sPDE V are of particular importance in human prostatic muscles: After performing Q-sepharose chromatography, there has been found a typical pattern of the human prostatic tissue showing the presence of the PDE isoforms I, IV and V (figure 1). A well-aimed inhibition of these isoenzymes will result in relaxation of the prostatic muscles even when minute doses of a specific inhibitor are administered, with no appreciable effects in other organ strips, in particular vessels, being observed. Therefore, they have an excellent efficiency in the treatment of prostatic diseases.

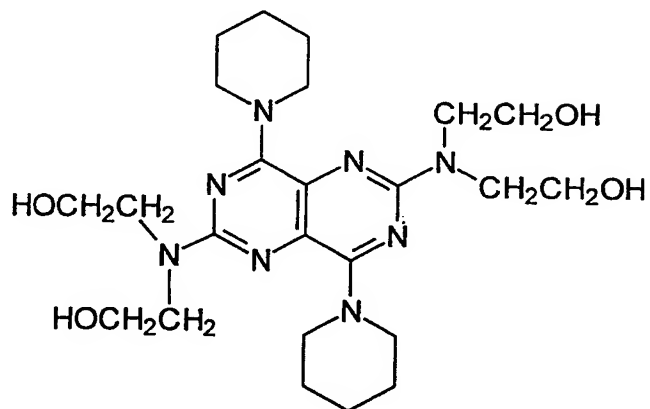
Therefore, the subject matter of the invention is the use of specific inhibitors of sPDE I, sPDE IV and sPDE V in the prophylaxis and treatment of prostatic diseases, in particular benign prostatic hyperplasia, the so-called urge symptoms, pollacuria (frequent micturition), nycturia (nocturnal micturition), weakened urine jet, urge incontinence (involuntary discharge of urine), prostatism, instabilities of the bladder muscles, impotence, and the use of the inhibitors for the preparation of medicaments useful for this purpose as well as medicaments containing sPDE I, IV and V inhibitors for the objects mentioned.

Preferred selective inhibitors of PDE I, IV and V are:

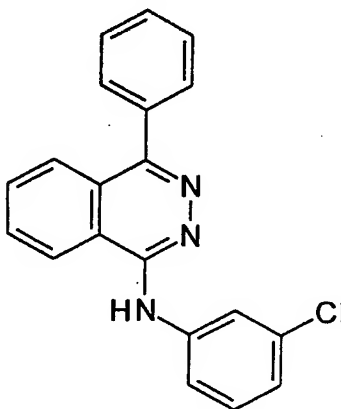
- a) 2-(2-propoxyphenyl)-8-azapurin-6-one (zaprinast);



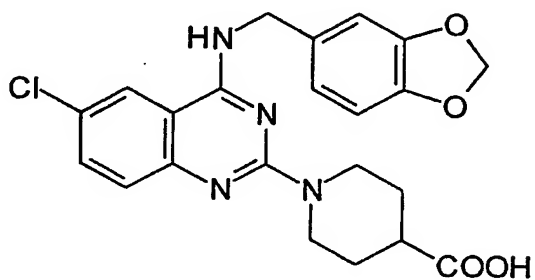
- b) dipyridamole;



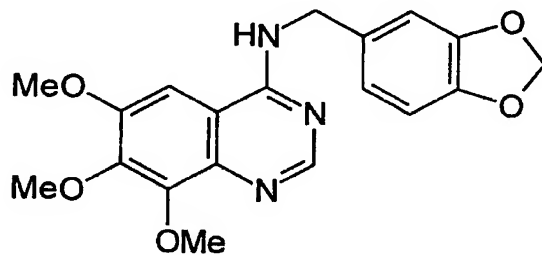
- c) 1-(3-chlorophenylamino)-4-phenylphthalazine (MY5445);



- d) 2-(N-(4-carboxypiperidine)-6-chloro-4-(3,4-(methylenedioxy)benzyl)amino)quinazoline (E 4021, ER 21355);

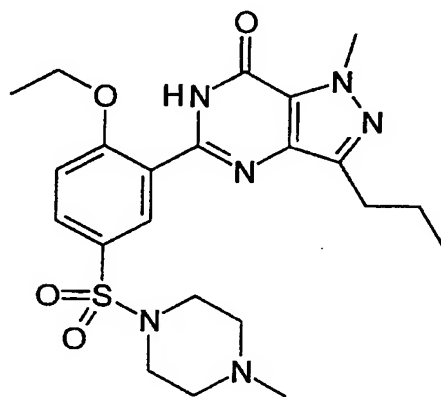


- e) 2,3-dihydro-8-hydroxy-7-nitro-1,4-benzodioxine-2-methanol, alpha-nitrate (E 4701);
- f) 4-((3,4-(methylenedioxy)benzyl)amino)-6,7,8-trimethoxyquinazoline;

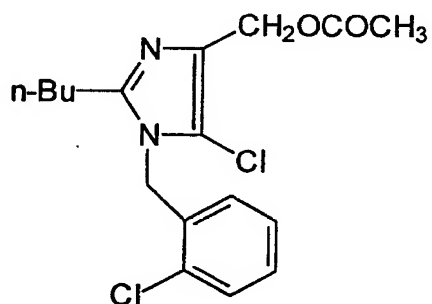


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- g) 1-methyl-3-propyl-6-(5-(N-(4-methylmorpholino)sulfonyl)-2-ethoxyphenyl)pyrazole[4,5]pyrimidin-4(5H)one (Sildenafil);

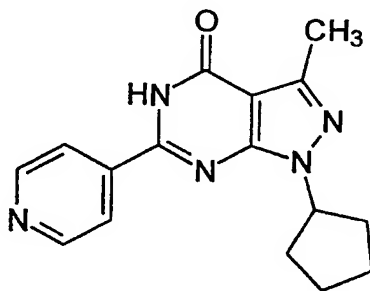


- h) 2-n-butyl-5-chloro-1-(2-chlorobenzyl)4-methylacetate-imidazole;

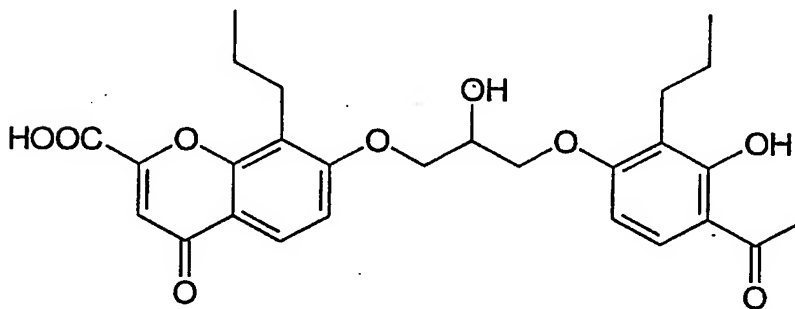


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- i) 1-cyclopentyl-3-methyl-6-(4-pyridinyl)pyrazolo(3,4-d)pyrimidin-4(5H)-one (WIN 58237);



- j) 7-(3-(4-acetyl-3-hydroxy-2-propyl-phenoxy)-2-hydroxy-propoxy)-2-carboxy-2,3-didehydro-chronan-4-one (FPL-55712);



- k) quinazolines and their trimethoxy derivatives;
 l) pyrazolopyrimidones;
 as well as pharmacologically compatible salts thereof.

The pharmacologically compatible salts are obtained in a similar manner by neutralizing the bases with inorganic or organic acids. As the inorganic acids, there may be used, for example, hydrochloric acid, sulfuric acid, phosphoric acid or hydrobromic acid, and as the organic acids, for example, carboxylic, sulfo or sulfonic acids, such as acetic acid, tartaric acid, lactic acid, propionic acid, glycolic acid, malonic acid, maleinic acid, fumaric acid, tannic acid, succinic acid, alginic acid, benzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, cinnamic acid, mandelic acid, citric acid, malic acid, salicylic acid,

3-aminosalicylic acid, ascorbic acid, embonic acid, nicotinic acid, isonicotinic acid, oxalic acid, amino acids, methane-sulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-methyl-benzenesulfonic acid, or naphthalene-2-sulfonic acid.

In the preparation of the medicaments for the treatment of the diseases mentioned, an effective amount of the inhibitors of sPDE I, IV or V or of the salts thereof is used in addition to the usual excipients, vehicles and additives. The dosage depends on the species, body weight, age, individual condition, and kind of administration.

Possible dosage forms are oral, intravenous, transdermal, subcutaneous and intravesicular formulations. The latter are, in particular, those solutions and formulations which are also used for parenteral administration.

Formulations for parenteral administration will contain from 0.15 μg to 1 mg, preferably from 5 to 500 μg , of the compounds mentioned per unit dose and may be present in separate unit dose forms, such as ampoules or vials. Preferably, solutions of the active ingredient are used, more preferably aqueous solutions, and mainly isotonic solutions, but also suspensions. These injection forms may be provided as a ready preparation, or they may be formulated only immediately before use by admixing the active compound, for example, the lyophilizate, optionally together with other solid carriers, with the solvent or suspension medium desired.

For oral administration, there are used the usual galenic preparations, such as tablets, coated tablets, capsules, dispersible powders, granules, aqueous or oily suspensions, syrups, liquors or drops.

Solid preparations may contain inert excipients and vehicles, such as calcium carbonate, calcium phosphate, sodium phosphate, lactose, starch, mannitol, alginates, gelatin, guar gum, magnesium or aluminium stearate, methylcellulose, talcum, highly dispersed silicic acids, silicone oil, higher-molecular fatty acids (such as stearic acid), agar-agar, or vegetable or animal fats and oils, solid high-molecular polymers (such as polyethylene glycol); formulations useful for oral administration may optionally contain additional flavoring and/or sweetening agents.

Liquid preparations may be sterilized and/or may optionally contain additives, such as preservatives, stabilizers, wetting agents, penetration agents, emulsifiers, spreading agents, solubilizers, salts for adjusting the osmotic pressure or for buffering, and/or viscosity modifiers.

Such additives are, for instance, tartrate and citrate buffers, ethanol, complexing agents (such as ethylenediaminetetraacetic acid and its non-toxic salts). For adjusting the viscosity, there may be used high-molecular polymers, such as, for example, liquid polyethylene oxide, carboxymethylcelluloses, polyvinylpyrrolidones, dextrans, or gelatin. Solid vehicles are, for instance, starch, lactose, mannitol, methylcellulose, talcum, highly dispersed silicic acids, higher-molecular fatty acids (such as stearic acid), gelatin, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high-molecular polymers (such as polyethylene glycol).

Oily suspensions for parenteral or topical (in this case intravesicular) administrations may contain vegetable, synthetic or semisynthetic oils, such as, for instance, liquid fatty acid esters having from 8 to 22 carbon atoms in the fatty acid chains, for example, palmitic, lauric, tridecylic, margaric, stearic, arachic, myristic, behenic, pentadecylic, linolic, elaidic, brassidic, erucic or oleic acids, which may be esterified with

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monohydric to trihydric alcohols having from 1 to 6 carbon atoms, such as, for instance, methanol, ethanol, propanol, butanol, pentanol, or isomers thereof, glycol, or glycerol. Such fatty acid esters are, for instance, commercially available miglyols, isopropyl myristate, isopropyl palmitate, isopropyl stearate, PEG 6-caprylic acid, caprylates/caprates of saturated fatty alcohols, polyoxyethyleneglycerol trioleates, ethyl oleate, waxy fatty acid esters, such as synthetic duck uropygial fat, coconut oil fatty acid isopropyl ester, oleic acid oleyl ester, oleic acid decyl ester, lactic acid ethyl ester, dibutyl phthalate, adipic acid diisopropyl ester, polyol fatty acid ester, etc. Also useful are silicone oils of various viscosities or fatty alcohols, such as isotridecyl alcohol, 2-octyldodecanol, cetylstearyl alcohol or oleyl alcohol, fatty acids, such as oleic acid. Further, vegetable oils, such as castor oil, almond oil, olive oil, sesame oil, cottonseed oil, peanut oil or soybean oil, may be used. The materials mentioned have the additional property of a spreading agent, i.e. there will be a particularly good spreading on the skin.

As solvents, gelling agents and solubilizers, there may be used water or water-miscible solvents. Useful are alcohols, for example, such as ethanol or isopropyl alcohol, benzyl alcohol, 2-octyldodecanol, polyethyleneglycols, phthalates, adipates, propylene glycol, glycerol, dipropylene or tripropylene glycol, waxes, methylcellosolve, cellosolve, esters, morpholines, dioxane, dimethylsulfoxide, dimethylformamide, tetrahydrofurane, cyclohexanone, etc.

As film-forming agents, there may be used cellulose ethers which can dissolve or swell both in water and in organic solvents and will form a kind of film after drying, such as hydroxypropyl-cellulose, methylcellulose, ethylcellulose, or soluble starches. Mixed gelling and film-forming agents are also possible by all means. In this case, there are chiefly used ionic macromolecules,

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such as sodium carboxymethylcellulose, polyacrylic acid, polymethacrylic acid, and salts thereof, sodium amylopectine semiglycolate, alginic acid or propylene glycol alginate as the sodium salt, gum arabic, xanthan gum, guar gum or carrageen.

As additional formulation aids, there may be used: glycerol, paraffins having different viscosities, triethanolamine, collagen, allantoin, novantisolic acid, perfume oils.

The use of surfactants, emulsifiers or wetting agents may also be required for the formulation, such as, for example, sodium lauryl sulfate, fatty alcohol ether sulfates, disodium N-lauryl β -iminodipropionate, polyoxyethylated castor oil, or sorbitan monooleate, sorbitan monostearate, cetyl alcohol, lecithin, glycerol monostearate, polyoxyethylene stearate, alkylphenol polyglycol ether, cetyltrimethylammonium chloride, or monoalkyl/dialkyl polyglycol ether ortho-phosphoric acid monoethanolamine salts.

Stabilizers, such as montmorillonites or colloidal silicic acids, for the stabilization of emulsions or for preventing decomposition of active substances, such as antioxidants, for example, tocopherols or butylhydroxyanisol, or preservatives, such as p-hydroxybenzoic acid ester, may also be required for the preparation of the formulations desired.

For promoting penetration, intravesicular formulations preferably contain highly compatible organic solvents, such as ethanol, methylpyrrolidone, polyethylene glycol, oleyl alcohol, octanol, linolic acid, triacetin, propylene glycol, glycerol, solketal, or dimethylsulfoxide.

The preparation, filling and sealing of the preparations is done under the usual antimicrobial and aseptic conditions. Also for topical or transdermal application, the preparations are

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preferably packed in separate unit doses for easy handling, and if required for stability reasons, as with parenteral forms, also by separately packing the active ingredients or their combinations as lyophilizates, optionally with solid carriers, and the solvents required etc.

Example 1 - Injection

Fifty milligrams of sildenafil is dissolved in distilled water together with 750 mg of NaCl, the pH is adjusted to 3.7 with 1 N HCl, distilled water is added to give a total of 100 ml, and the solution is packed in 0.5 ml ampoules.

Example 2 - Solution for Topical Administration

From 500 mg of sildenafil, 2 ml of isopropyl myristate and 10 ml of ethanol, a solution for topical administration is prepared and packed in unit doses of 2 ml each.

The effectiveness of the medicaments according to the teaching of the invention is demonstrated by the following pharmacological studies:

Human prostatic tissue freshly collected in the course of an operation is cut into small strips (about 3 x 3 x 6 mm). The latter are then installed in a bath containing a nutrient solution ensuring survival of the organic strips. By coupling the organic strips to a measuring element, length and force changes of the organic strip can be recorded, and thus actions of medicaments added to the organ bath nutrient solution can be examined through the length and force changes (increase or decrease) of the organic strip. At the beginning of the experiment, the organic strips are contracted with an appropriate standard medicament (e.g., carbachol). After the contraction of the organic strips is completed, an inhibitor of a specific

phosphodiesterase is now added in incremental dosage (10^{-8} , 10^{-7} , 10^{-6} etc. mol/l) to the organ bath solution, and the relaxation triggered thereby is measured. The results obtained are essentially applicable to the whole organism since human tissue had been used and the metabolic processes studied proceed faster in the whole organism and thus the medicaments will act still more quickly. In these studies, the inhibitors of PDE I, IV and V proved to have the strongest prostatic tissue relaxing effect.

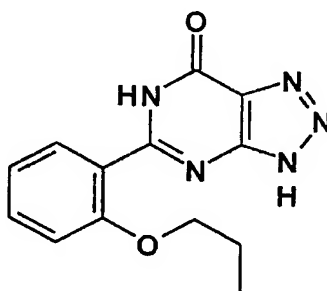
The proof of whether a compound is suitable for the purpose according to the invention, i.e. is an inhibitor of sPDE I, IV or V, is furnished by known methods, such as described, e.g., by Galwan et al., Arch. Pharmacol. 1990, 342, 221-227; or Nicholson, Br. J. Pharmacol. 1989, 79, 889-897; for example, according to the following general procedure:

Fresh tissue obtained during an operation is homogenized and then ultracentrifuged. Next, the supernatant is filtered, pipetted off and chromatographed. The determination of sPDE is performed as described in M. Truss et al.: Urology 45(5): 893-901, 1995. The determination of the amount of radioactivity permits to calculate the enzyme activity in pmol/ml x min. A plot of the activity curve allows to identify fractions in which the phosphodiesterase activity is particularly high. The phosphodiesterase activity of each peak exhibits a different composition with respect to the activity of the different substrates. This special composition of the phosphodiesterase activity allows for the assignment to a specific phosphodiesterase (sPDE). A substance is considered an inhibitor of an sPDE if the concentration thereof which is necessary for inhibiting 50% of the substrate hydrolysis (IC_{50}) is at least 20 times lower in the respective peak fraction containing the specific phosphodiesterase than in other peak fractions. For this purpose, enzyme preparations are again prepared, as described above. Now, however, the compound to be tested is added prior to the incubation of the enzyme mixtures

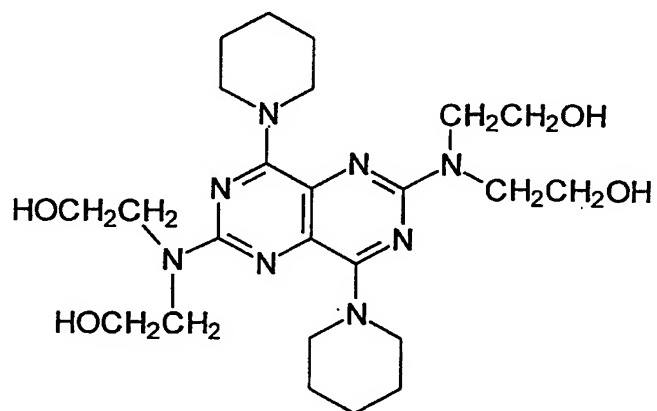
according to peak fractions. Then, renewed determination and plotting of the enzyme activity allows to identify a substance as being an inhibitor of the specific phosphodiesterase according to the above-mentioned definition.

C L A I M S :

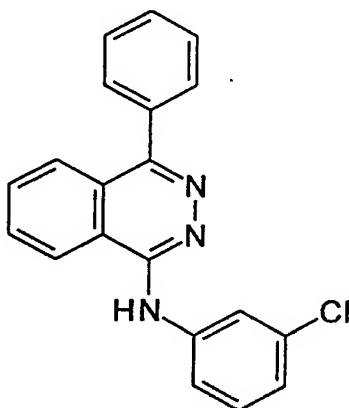
1. Use of a component in the prophylaxis and treatment of prostatic diseases, in particular benign prostatic hyperplasia, the so-called urge symptoms, pollacuria (frequent micturition), nycturia (nocturnal micturition), weakened urine jet, urge incontinence (involuntary discharge of urine), prostatism, instabilities of the bladder muscles and impotence selected from the group of
 - a) 2-(2-propoxyphenyl)-8-azapurin-6-one (zaprinast);



b) dipyridamole;

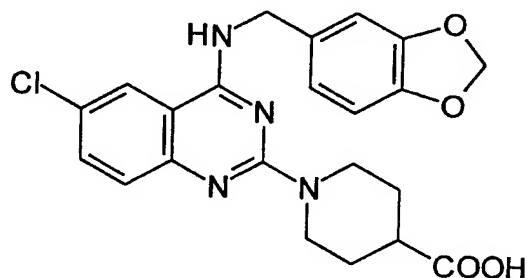


c) 1-(3-chlorophenylamino)-4-phenylphthalazine (MY5445);

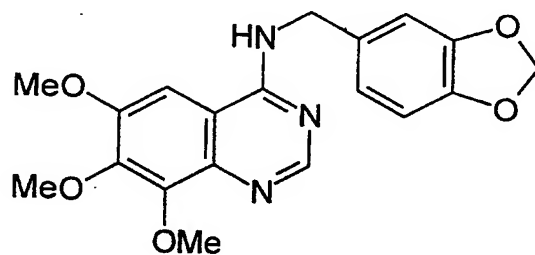


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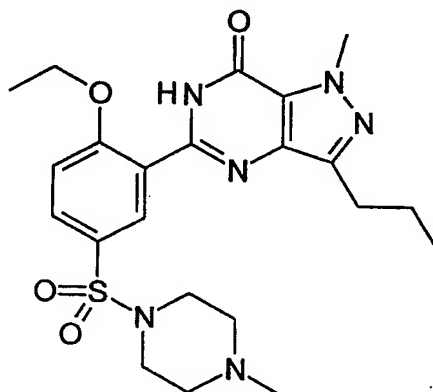
- d) 2-(N-(4-carboxypiperidine)-6-chloro-4-(3,4-(methylenedioxy)benzyl)amino)quinazoline (E 4021, ER 21355);



- e) 2,3-dihydro-8-hydroxy-7-nitro-1,4-benzodioxine-2-methanol, alpha-nitrate (E 4701);
- f) 4-((3,4-(methylenedioxy)benzyl)amino)-6,7,8-trimethoxyquinazoline;

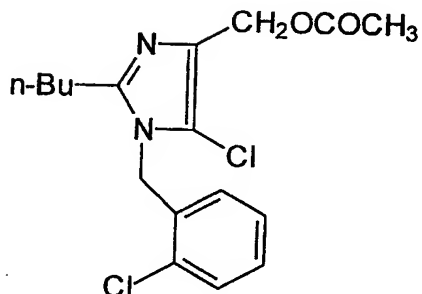


- g) 1-methyl-3-propyl-6-(5-(N-(4-methylmorpholino)sulfonyl)-2-ethoxyphenyl)pyrazole[4,5]pyrimidin-4(5H)one (Sildenafil);

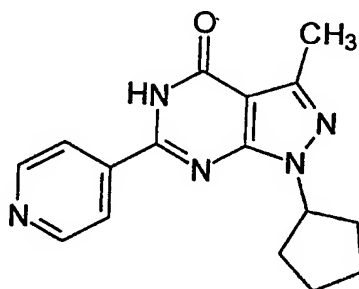


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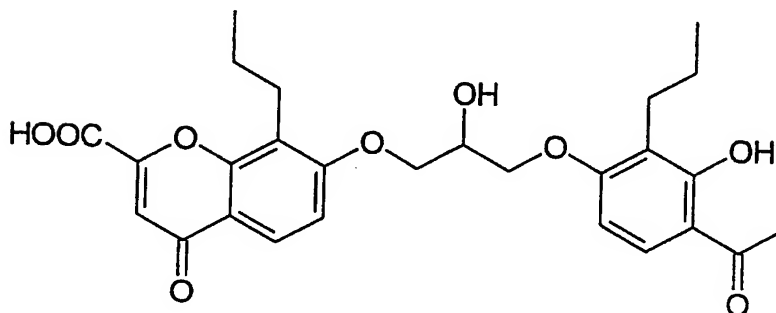
- h) 2-n-butyl-5-chloro-1-(2-chlorobenzyl)-4-methylacetate-imidazole;



- i) 1-cyclopentyl-3-methyl-6-(4-pyridinyl)pyrazolo(3,4-d)pyrimidin-4(5H)-one (WIN 58237);



- j) 7-(3-(4-acetyl-3-hydroxy-2-propyl-phenoxy)-2-hydroxy-propoxy)-2-carboxy-2,3-didehydro-chroman-4-one (FPL-55712);

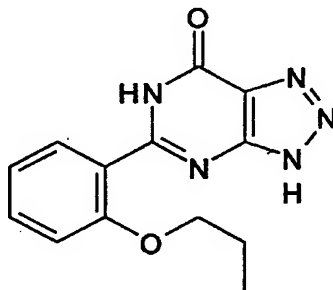


- k) quinazolines and their trimethoxy derivatives;
l) pyrazolopyrimidones;

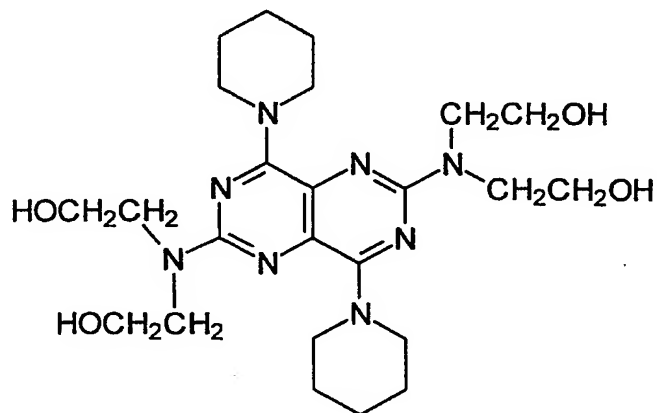
as well as pharmacologically compatible salts thereof.

2. Medicaments for the prophylaxis and treatment of prostatic diseases, in particular benign prostatic hyperplasia, the so-called urge symptoms, pollacuria (frequent micturition), nycturia (nocturnal micturition), weakened urine jet, urge incontinence (involuntary discharge of urine), prostatism, instabilities of the bladder muscles, and impotence, containing a component selected from the group of

- a) 2-(2-propoxyphenyl)-8-azapurin-6-one (zaprinast);

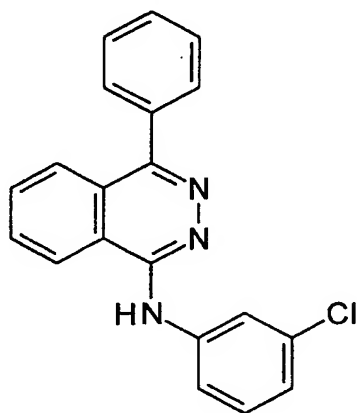


- b) dipyridamole;

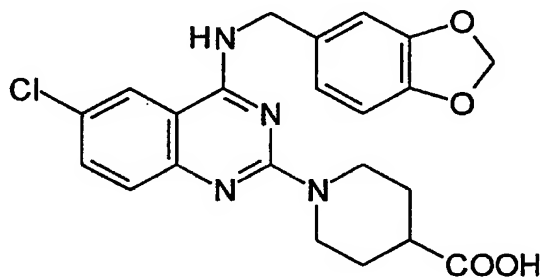


- 20 -

- c) 1-(3-chlorophenylamino)-4-phenylphthalazine (MY5445);

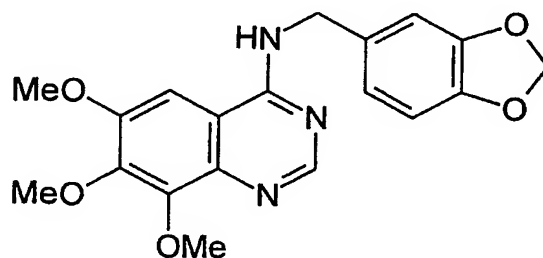


- d) 2-(N-(4-carboxypiperidine)-6-chloro-4-(3,4-(methylenedioxy)benzyl)amino)quinazoline (E 4021, ER 21355);

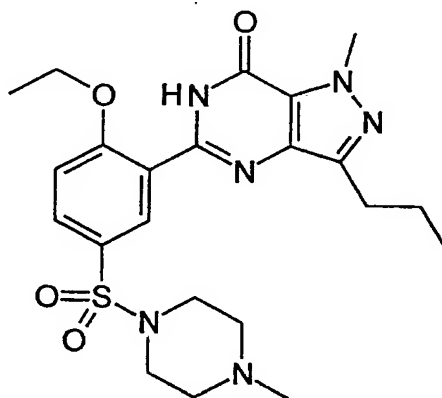


- e) 2,3-dihydro-8-hydroxy-7-nitro-1,4-benzodioxine-2-methanol, alpha-nitrate (E 4701);

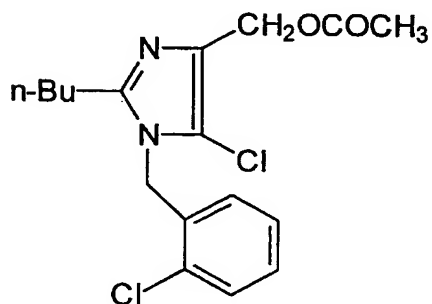
- f) 4-((3,4-(methylenedioxy)benzyl)amino)-6,7,8-trimethoxyquinazoline;



- g) 1-methyl-3-propyl-6-(5-(N-(4-methylmorpholino)sulfonyl)-2-ethoxyphenyl)pyrazole[4,5]pyrimidin-4(5H)one (Sildenafil);

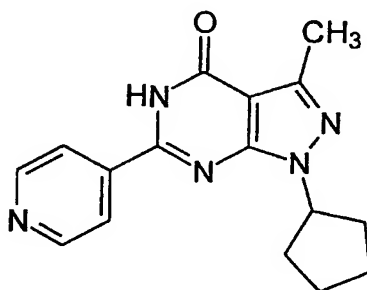


- h) (2-n-butyl-5-chloro-1-(2-chlorobenzyl)4-methylacetate-imidazole;

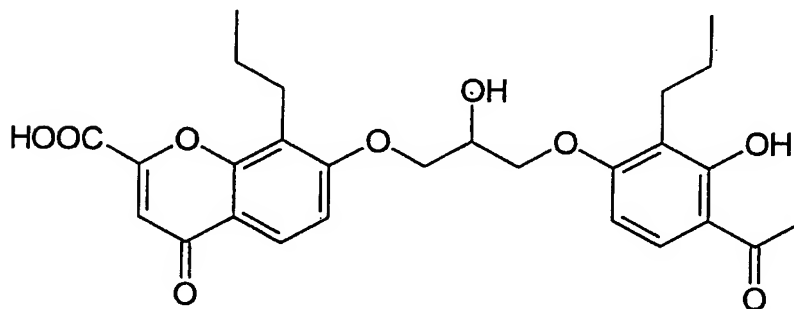


- 22 -

- i) 1-cyclopentyl-3-methyl-6-(4-pyridinyl)pyrazolo(3,4-d)pyrimidin-4(5H)-one (WIN 58237);



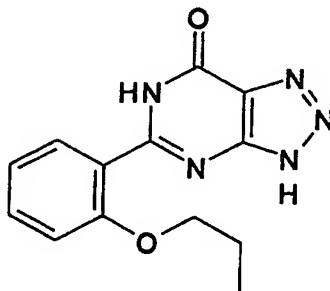
- j) 7-(3-(4-acetyl-3-hydroxy-2-propyl-phenoxy)-2-hydroxy-propoxy)-2-carboxy-2,3-didehydro-chroman-4-one (FPL-55712);



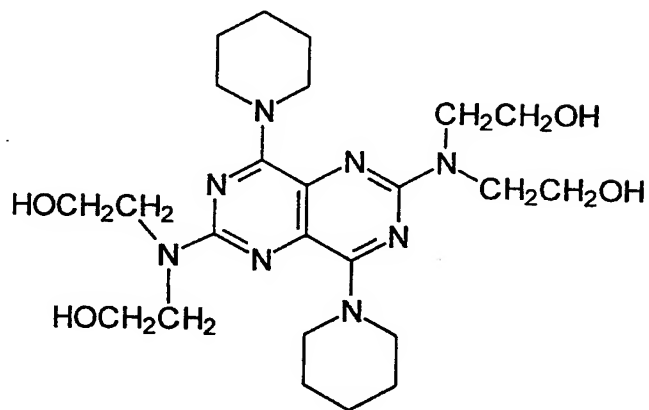
- k) quinazolines and their trimethoxy derivatives;
 l) pyrazolopyrimidones;
 as well as pharmacologically compatible salts thereof.

3. Use of a component in the preparation of medicaments for the prophylaxis and treatment of prostatic diseases, in particular benign prostatic hyperplasia, the so-called urge symptoms, pollacuria (frequent micturition), nycturia (nocturnal micturition), weakened urine jet, urge incontinence (involuntary discharge of urine), prostatism, instabilities of the bladder muscles, and impotence, selected for the group of

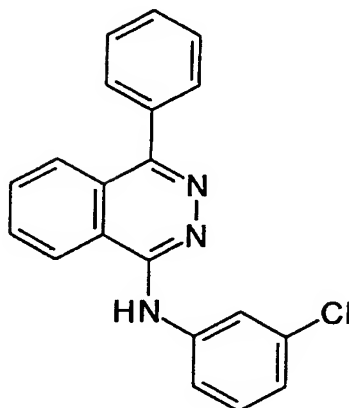
- a) 2-(2-propoxyphenyl)-8-azapurin-6-one (zaprinast);



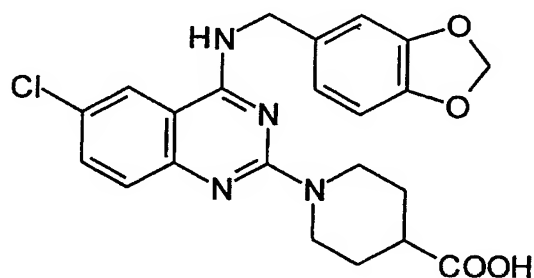
- b) dipyridamole;



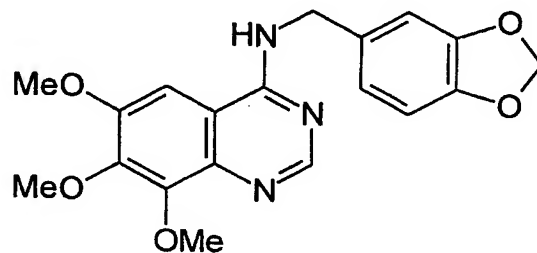
- c) 1-(3-chlorophenylamino)-4-phenylphthalazine (MY5445);



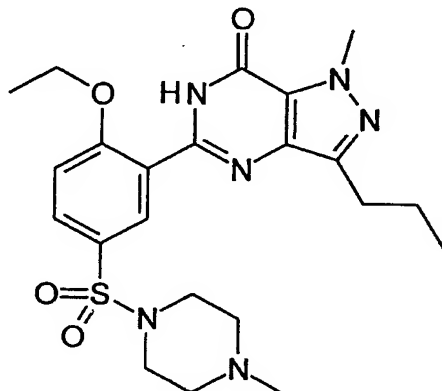
- d) 2-(N-(4-carboxypiperidine)-6-chloro-4-(3,4-(methylenedioxy)benzyl)amino)quinazoline (E 4021, ER 21355);



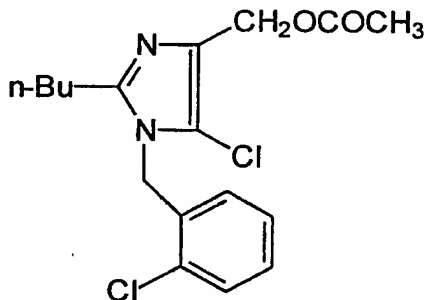
- e) 2,3-dihydro-8-hydroxy-7-nitro-1,4-benzodioxine-2-methanol, alpha-nitrate (E 4701);
- f) 4-((3,4-(methylenedioxy)benzyl)amino)-6,7,8-trimethoxyquinazoline;



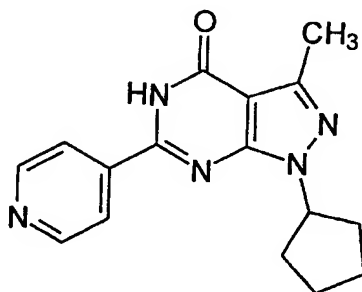
- g) 1-methyl-3-propyl-6-(5-(N-(4-methylmorpholino)sulfonyl)-2-ethoxyphenyl)pyrazole[4,5]pyrimidin-4(5H)one (Sildenafil);



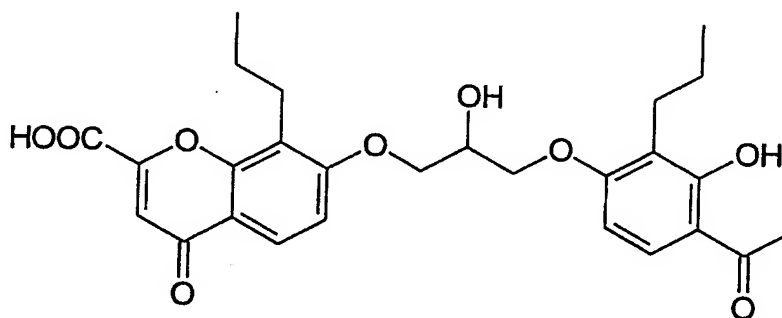
- h) (2-n-butyl-5-chloro-1-(2-chlorobenzyl)4-methylacetate-imidazole;



- i) 1-cyclopentyl-3-methyl-6-(4-pyridinyl)pyrazolo(3,4-d)pyrimidin-4(5H)-one (WIN 58237);



- j) 7-(3-(4-acetyl-3-hydroxy-2-propyl-phenoxy)-2-hydroxy-propoxy)-2-carboxy-2,3-didehydro-chronan-4-one (FPL-55712);



- k) quinazolines and their trimethoxy derivatives;
l) pyrazolopyrimidones;
as well as pharmacologically compatible salts thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/03617

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/52 A61K31/505 A61K31/50 A61K31/415 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 195 40 642 A (STIEF CHRISTIAN GEORG PRIV DOZ) 7 May 1997 see column 2, line 40 - line 66 see claims 1-5 -----	1-3

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"G" document member of the same patent family

Date of the actual completion of the international search

30 January 1998

Date of mailing of the international search report

13.02.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Trifilieff-Riolo, S

INTERNATIONAL SEARCH REPORT

I. International application No.

PCT/EP 97/03617

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 1 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Internal Application No.

PCT/EP 97/03617

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19540642 A	07-05-97	NONE	